

REMARKS

Applicant acknowledges that rejections and/or objections not reiterated from the previous Office Action have been withdrawn by the Examiner.

Claims 231 and 316-324 are pending in this application. Claim 231 is amended by the addition of a comma. Claim 317 is amended to correct a typographical error. No new matter has been added. As a result, claims 231 and 316-324 are pending for examination with Claim 231 being an independent claim.

Claim Rejections under 35 U.S.C. §112

The Examiner has required clarification of claim 231. Claim 231 is directed to a pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof. In addition to the methylnaltrexone or salt thereof, the preparation also comprises a chelating agent. To further clarify the instant claim, Applicant has amended it by inserting a comma following the phrase “methylnaltrexone or a salt thereof” and adding a paragraph break following “and”. Accordingly, Applicant respectfully requests a withdrawal of the instant rejection.

Claim Rejections under 35 U.S.C. §103

Claims 231 and 316-324 are rejected under 35 USC 103(a) as being unpatentable over Moss et al., Patent Application Publication US 2003/0022909A1 ('909) in view of Remington's Pharmaceutical Sciences (1975), (Remington's).

The Examiner states that Moss et al teach a solution comprising methylnaltrexone (“MNTX”); the Examiner acknowledges that Moss et al. does not teach either the claimed pH or a chelating agent. However, the Examiner notes that Moss et al teaches buffering agents such as citric acid in a concentration of 1-3% w/v. The Examiner then states that Remington's teaches that citric acid can be used for the purpose of sequestering metals. According to the Examiner, Remington's also teaches that EDTA can be used to sequester metals and “one of ordinary skill in the art could have substituted one known chelating/sequestering agent for another, and the results of the substitution would have been predictable”.

Reconsideration is requested. Respectfully, it is believed that the Examiner has not made a *prima facie* case for rejecting the claims.. Moss et al describe pharmaceutical compositions of

peripheral opioid antagonists that “may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients” (paragraph [0071]). Lists of potentially suitable salts, buffering agents, preservatives, carriers, and other therapeutic ingredients are provided. Moss et al, therefore, explicitly indicate items that are “substitutable” for one another as buffering agents. In order to levy this rejection, the Examiner has to take the position that one of ordinary skill would read Moss et al’s list of buffering agents and decide to “substitute” something that is *not* a buffering agent. Citric acid is a buffering agent; EDTA is not. Even if it is correct that citric acid can, at least in some contexts, act as a sequestering agent, it is also the case that citric acid is a buffering agent. Moss et al teach that the *buffering* capacity of citric acid is useful in the context of Moss et al’s invention. It would not have been obvious to one of ordinary skill in the art, as suggested by the Examiner, to “substitute” an agent (e.g., EDTA) that *does not buffer* for an agent (e.g. citric acid) taught to be useful in the Moss et al invention solely as a result of its capacity as a buffering agent.

Moreover, the Examiner’s assertion that “the results of the substitution would have been predictable” cannot be correct. Setting aside for the moment the fact that the Examiner has not provided any evidence that the citric acid buffer described by Moss et al. would sequester metals under the conditions of Moss et al., the Examiner’s own characterization of the proposed substitution would remove an agent (citric acid) intended as a buffer and that can *both* buffer *and* sequester metals, and would replace it with an agent (EDTA) that can *only* sequester metals. It is not at all predictable from Moss et al and Remington’s what would happen if such a change were made in any solution containing peripheral opioid antagonists, let alone in a solution of MNTX, as recited in the present claims.

Still further, the present claims recite a composition that *both* includes a chelating agent *and* a pH between 2 and 6. The “substitution” proposed by the Examiner clearly would not create such a composition, as it would *remove* the buffering agent from the solution.

The Examiner presents an argument that, because certain art shows that morphine solutions with a pH of less than 5.5 are stable during sterilization at 100 °C, whereas neutral and alkaline solutions are highly unstable, one of ordinary skill would be motivated to employ a pH of between 2 and 6 for solutions of MNTX. While it is certainly true that morphine shares some structural similarity with MNTX, this fact does not mean that the two compounds would

necessarily be expected to be stabilized under the same conditions for the simple reason that the two compounds also have some structural *differences*, which structural differences can lead to different degradation pathways.

To give but one example, Applicant encloses herewith in an Information Disclosure Statement, a reference by Vermeire et al., which describes morphine degradation. As shown, oxidation is one of the main degradation mechanisms of morphine. Such oxidation results in the formation of morphine-*N*-oxide. As is readily apparent, the single nitrogen atom present in MNTX is quaternized and, therefore, unable to be oxidized. Thus, it is respectfully submitted that one of ordinary skill in the art would not have expected that a strategy to protect against the degradation of morphine would be a successful approach to protecting against methylnaltrexone degradation. For all of these reasons, it is clear that the Examiner has not made out a *prima facie* case of obviousness.

Moreover, even had the Examiner provided evidence of *prima facie* obviousness, the present invention demonstrates unexpected results. Specifically, the present specification demonstrates that, whatever different approaches one of ordinary skill in the art might explore in the stabilization of methylnaltrexone solutions, the particular combination of a chelating agent and a pH between 2 and 6 shows unexpected improvements. Indeed, Applicant discovered a previously unrecognized problem that MNTX solutions were not stable under various conditions. The problem was unexpected given that methylnaltrexone had been studied since the late 1970s (see U.S. Patent 4,176,186), yet it was not known that solutions of methylnaltrexone are not stable under certain conditions. Case law clearly establishes that an inventor who identifies a problem is entitled to a patent embodying the remedy. In its famous decision in *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923), no less authority than the Supreme Court held that:

“It was the discovery of the source [of a problem] not before known, and the application of the remedy, for which Eibel was entitled to be rewarded in his patent.”

See Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45 at 63.¹ Similarly, in *In re Sponnoble*, 405 F.2d 578 (C.C.P.A. 1969), the Court of Customs and Patent Appeals held that:

“a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified.”

See In re Sponnoble, 405 F.2d 578 at 585.

In the present case, however, the solution is not obvious because, in solving the newly-identified problem, Applicant further discovered unexpected benefits of combining a particular pH range and a chelating agent. The unexpected solution to the newly identified problem is clearly recited in the present claims, which are directed to (1) solutions of MNTX that (2) contain a chelating agent; and (3) have a pH between 2 and 6. Applicant respectfully submits that the present claims are not obvious, and requests withdrawal of the instant rejection.

¹ *See also In re Peehs*, 612 F.2d 1287 (C.C.P.A. 1980).

Conclusion

In view of the foregoing remarks, this application is believed to be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes that the application is not in condition for allowance, the Examiner is requested to call Applicant's attorney at the number listed below.

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Respectfully submitted,

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